

AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 06: Developmental Delays, ADHD, and Autism

Prepared for:

Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
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Contract No. HHSA290201000006C

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June 2013

Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290201000006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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Financial Disclosure Statement

None of the individuals compiling this information has any affiliations or financial involvement that conflicts with the material presented in this report.

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Suggested citation: ECRI Institute. AHRQ Healthcare Horizon Scanning System Potential High-Impact Interventions: Priority Area 06: Developmental Delays, ADHD, and Autism. (Prepared by ECRI Institute under Contract No. HHSA290201000006C.) Rockville, MD: Agency for Healthcare Research and Quality. June 2013. <http://www.effectivehealthcare.ahrq.gov/reports/final.cfm>

Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High-Impact Interventions report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to: effectivehealthcare@ahrq.hhs.gov.

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Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identifying new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 4 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 16,000 leads about potential topics has resulted in identification and tracking of about 1,800 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 600 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice annually. Topics eligible for inclusion are those interventions expected to be within 0–4 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 350 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the seven or eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts’ rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of “lower,” “moderate,” or “higher” within the high-impact-potential range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received, and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ’s Effective Health Care Web site.

Results

The table below lists one topic for which (1) preliminary data were available; (2) information was compiled by May 16, 2013, in this priority area; *and* (3) we received five to nine sets of comments from experts between October 25, 2011, and May 18, 2013. (Seven topics in this priority area were being tracked in the system as of May 18, 2013.) This one topic emerged as having moderate high-impact potential on the basis of experts’ comments and their assessment of potential impact. Readers are also encouraged to read the detailed information on the intervention that follows the Executive Summary.

Priority Area 06: Developmental Delays, ADHD, and Autism

Topic	High-Impact Potential
1. *Off-label intranasal oxytocin (Syntocin) for treatment of social dysfunction in autism spectrum disorders	Moderately high

Discussion

Although we perform intensive scanning for interventions and innovations in this priority area, we find a paucity of leads on innovations. The dearth of topics on diagnosis, treatment, and services for developmental disorders including attention-deficit hyperactivity disorder and autism spectrum disorders (ASDs) implies a lack of progress in basic understanding of these disorders and how to diagnose and treat them. Nevertheless, one topic emerged as having potential for high impact and purports to address the problem of social dysfunction in individuals with ASD.

ASDs, also sometimes referred to as pervasive developmental disorders, are a wide continuum of associated cognitive and neurobehavioral disorders that have three core-defining features: impairments in socialization, impairments in verbal and nonverbal communication, and restricted and repetitive patterns of behavior. Experts think that the earlier a definitive diagnosis can be established and the earlier that intervention can begin, the better chance an affected child has of improving cognitive development and social functioning. Current early-intervention treatment for ASDs include providing highly structured behavioral programs to try to improve social cognition and functioning, using technology such as computer tablets and tools such as animated dolls, and

prescribing pharmacologic therapies to address symptoms. To date, effective pharmacologic treatments for social deficits in individuals with ASD are lacking.

One topic that emerged as having potential is use of off-label intranasal oxytocin to treat social dysfunction in ASDs.

Off-Label Intranasal Oxytocin (Syntocin) for Treatment of Social Dysfunction in Autism Spectrum Disorders

- **Key Facts:** Most individuals with an ASD are treated through highly structured behavior programs to try to improve social cognition and functioning. However, effective pharmacologic treatments for social deficits in individuals with ASD are lacking. Having an effective medication targeted at the core social deficits of ASD in early childhood could affect developmental pathways to make other psychosocial interventions possible. In humans, oxytocin is produced and synthesized in the paraventricular and supraoptic nuclei of the hypothalamus and stored in the pituitary gland. Once synthesized, oxytocin acts as a neurotransmitter on several central target areas, including the amygdala, an area responsible for social and emotional behavior. Although this hormone is best known for inducing childbirth and lactation, researchers have investigated oxytocin's role in improving social behavior, particularly social cognition. In ongoing and completed trials, study results have suggested increased oxytocin levels in the body were associated with positive effects on social interactions. Several institutions are investigating intranasal oxytocin for treating social cognitive deficits in patients with ASD. Manufacturers may have pursued regulatory approval of intranasal oxytocin for this indication, but our searches for information could not confirm that. Currently, an oxytocin nasal spray 5 mL (40 IU/mL) bottle is available for use in the United States and may be prescribed off-label.
- **Key Expert Comments:** Overall, experts commenting on this intervention agreed that an unmet need exists for an effective treatment for social dysfunction in ASD; however, they thought that more data would be necessary before widespread adoption could occur. Still, the experts believe there is great potential for intranasal oxytocin to become the standard of care for treating social dysfunction in ASDs, given the absence of other medication options for this indication.
- **Potential for High Impact:** Moderately high

Developmental Delays, ADHD, and Autism, Intervention

Off-Label Intranasal Oxytocin (Syntocin) for Treatment of Social Dysfunction in Autism Spectrum Disorders

Unmet need: Autism spectrum disorders (ASDs) are a group of developmental brain disorders that show varying levels of cognitive impairment and a wide range of symptoms and skills.¹ ASD symptoms vary, but generally fall into one or more of three areas: social dysfunction, communication difficulties, and repetitive and stereotyped behaviors.² Children with social dysfunction symptoms may make little eye contact, look and listen less to people in their environment, fail to respond to other people, not express enjoyment of toys and activities by pointing or showing things to others, and may respond unusually when others show anger, distress, or affection.²

Most individuals with an ASD are treated through highly structured behavior programs to try to improve social cognition and functioning.² These programs may use technology such as computer tablets and animated dolls as part of the therapy. Pharmacologic therapies can address symptoms of hyperactivity and depression, but effective pharmacologic treatments for social deficits in individuals with ASD are lacking. Having an effective medication targeted at the core social deficits of ASD in early childhood could affect developmental pathways to make other psychosocial interventions possible.

Intervention: Oxytocin is a hormone composed of nine amino acids (cysteine-tyrosine-isoleucine-glutamine-asparagine-cysteine-proline-leucine-glycine-amine). In humans, this hormone is produced and synthesized in the paraventricular and supraoptic nuclei of the hypothalamus and stored in the pituitary gland.³ Once synthesized, oxytocin acts as a neurotransmitter on several central target areas, including the amygdala, an area responsible for social and emotional behavior. Once secreted from the pituitary gland, oxytocin exhibits peripheral effects that could also play a role in social behavior. Although this hormone is best known for inducing childbirth and lactation, researchers have investigated oxytocin's role in improving social behavior, particularly social cognition.⁴

Clinical trials: In ongoing and completed trials, intranasal oxytocin has been administered most often at a dose of 24 IU twice daily.⁵⁻⁸ Study results have suggested that increased oxytocin levels in the body were associated with positive effects on social interactions.⁹ According to results of one study, intranasal oxytocin has improved social cues in male patients with high-functioning autism or Asperger's syndrome.¹⁰ Although the exact mechanism of action is unclear, basing their opinions on preliminary study results, researchers believe that acute intranasal oxytocin (Pitocin®, Syntocinon®) administration might significantly improve social cognitive deficits and social functioning and reduce repetitive behavior in this patient population.¹¹ The U.S. Food and Drug Administration (FDA) has approved intranasal oxytocin for inducing uterine contractions in labor and inducing lactation, and thus it is available for use off label.

Manufacturer and regulatory status: Several institutions, including Children's Hospital of Philadelphia, PA; Montefiore Medical Center of Albert Einstein Hospital, New York, NY; Stanford University School of Medicine, CA; Holland Bloorview Kids Rehabilitation Hospital, Ontario, Toronto, Canada; and University of Sydney, Australia, are investigating intranasal oxytocin for treating social cognitive deficits in patients with autism.⁵⁻⁸

Manufacturers including Cypress Bioscience, Inc. (acquired by Royalty Pharma of New York City), and Pastorus Pharma, LLC, of Green River, WY, in collaboration with Shin Nippon Biomedical Laboratories, Ltd., of Tokyo, Japan, may have pursued regulatory approval of intranasal oxytocin for this indication, but our searches could not confirm this.^{12,13} Currently, an oxytocin

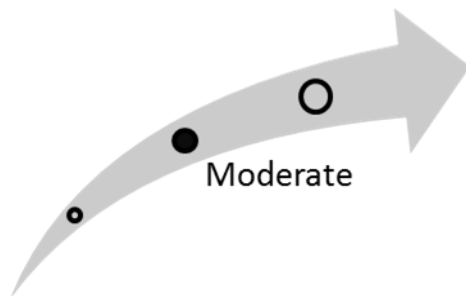
nasal spray 5 mL (40 IU/mL) bottle is available for use in the United States and may be prescribed off label.

Clinical Pathway at Point of This Intervention

Dietary and medical interventions used to control autism symptoms include antidepressants, antipsychotic medications, immune system moderators, and nutritional supplements (i.e., vitamins).^{14,15} Behavior and communication therapies have been used to reduce social cognitive deficits in patients with autism. In 2006, FDA approved risperidone (Risperdal®) for treating irritability in autistic children and in other children and adolescents aged 5–16 years. However, at this time, no medications are available that address and improve the core symptoms of ASD.¹⁴

Patients who are using oxytocin intranasal spray are expected to experience little modification to their routines and no staffing and infrastructure implications are expected to arise.

Figure 1. Overall high-impact potential: off-label intranasal oxytocin (Syntocin) for treatment of autism spectrum disorders



Overall, experts commenting on this intervention agreed that an unmet need exists for an effective treatment for social dysfunction in ASD, especially considering the debilitating nature of this condition to both the individual and the family or caretakers. Experts noted this intervention has the potential to address this unmet need; however, they indicated more data would be necessary before widespread adoption could occur. Still, the experts believe there is great potential for intranasal oxytocin to diffuse widely among providers and patients and potentially become the standard of care for treating social dysfunction in ASDs. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, provided comments on this topics.¹⁶⁻²¹ We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Experts agreed the unmet need for this intervention is significant; they cited lack of current treatments and the debilitating nature of social dysfunction in ASD (to both the individual and family or caretakers). No treatments are available to address social dysfunction, experts noted, adding that this intervention would present a safe and unobtrusive treatment mechanism.

Overall, experts noted the need for more data to show the efficacy and long-term effects of this intervention and as such, their opinions varied on the ability of oxytocin to meet this need. Some experts suggested the data are promising and others were more reserved about drawing conclusions yet. One expert with clinical experience stated, “The theoretic and empiric support for this therapy is better than some that have been tried in the past.”

Acceptance and adoption: Providers and patients are expected to eagerly adopt the treatment if sufficient data accumulate to prove it to be efficacious, experts agreed. They cited the convenience and low cost of oxytocin as well as the desperation of parents and clinicians for an effective treatment as potential drivers for diffusion. One expert suggested that if proven effective, this intervention has the potential to be the standard of care for ASDs.

Health care delivery infrastructure and patient management: Experts varied in their perceptions of the potential for this intervention to disrupt health care delivery and patient management. Because this intervention is an already-established pharmacologic agent, most of the experts did not think it likely to result cause any significant changes in infrastructure or staffing. They thought that oxytocin intranasal spray would just be added to existing treatment regimens. However, other experts concluded that this intervention would potentially reduce the need for other behavioral therapies and as a result, might also reduce costs of care.

Health disparities: Overall, experts believe the low cost of this intervention would allow it to be accessible across different groups and, therefore, have a minimal effect on health disparities. One expert noted that intranasal oxytocin use has the potential to reduce the stigma associated with ASDs, but another expert raised concerns about a potential disparity in the use of the intervention in female patients (because an approved indication for oxytocin is labor induction). But for the most part, the experts concluded intranasal oxytocin would neither contribute to nor reduce health disparities.

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